eight minutes, and yet the salicylates had not been discontinued. In two of the cases calcium lactate was given in 30 grain doses every four hours for two days without the clotting time being at all shortened. One case was complicated with pericarditis and another with quinsy, without any apparent effect upon the coagulation time.

Typhoid Fever. Sixty observations were made upon 26 cases of this disease, and the average clotting time was found to be 7.1 minutes, with a range of from 5 to 12 minutes. Two cases, which had phlebitis, and had been treated for four and seven days respectively, with large doses of citric acid (30 grains every four hours), showed a coagulation time of 5.3 and 7.1 minutes; 1 case showed a shortening in the clotting time of from 7.5 to 6.25 minutes following three days of profuse diarrhea. The severity of the invasion did not seem to have any effect upon the clotting time.

CONCLUSIONS. 1. The instrument used is a convenient one for clinical purposes, and gives, with constant technique, fairly constant results. Thus, if the coagulation time of an individual be estimated several times within a few minutes of each other the readings will seldom differ by more than a minute, and are usually within half that time of one another.

2. Coagulation time, as estimated *in vitro*, and a tendency to hemorrhage are not necessarily related to each other. Thus, a patient may have a fast clotting time and yet bleed freely from a slight lesion anywhere, the trouble being probably rather of vascular than of hemic origin.

3. The firmness of the coagulum is an important matter, and can be roughly gauged by this method, although the results cannot be given in figures.

4. Anemia due to hemorrhage is constantly associated with a hastened coagulation time.

5. Acute rheumatism is usually accompanied by a delay in the clotting.

6. The free exhibition of calcium lactate and of citric acid by the mouth in various diseased conditions seems to have no appreciable effect upon the coagulation time of the blood as estimated by this method.

THE PHYSIOLOGY AND PATHOLOGY OF FEVER.[1]

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OF all the symptoms which appear during the various pathological conditions of the human organism, fever, because of its frequency, occupies the first place. It is quite natural, therefore, that from days immemorial, it attracted the attention of physicians, who tried to explain it and the other disturbances that are connected with it. The subject presents interest not only from its practical point of view, but more so from its theoretical, because it is only after a thorough and clear understanding of the exact causes of fever that proper therapeutic measures may be applied. A great many clinicians and scientists studied these problems from their respective views, and the literature of the subject became burdened with facts. The clinician gathered information from the bed side; he watched the behavior of his patient under the influence of different infectious processes; studied them, and finally learned to recognize them from the character of the symptoms. The scientists attacked the problem from the other side. They produced the disease in animals experimentally by injecting different toxins, or produced one of the many symptoms of fever, and studied their influences on the organism.

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[1] Read before the Eastern Medical Society, New York.

In this brief review we will endeavor to present themost important facts and theories that have been accepted in the past few years. The first question that confronts an investigator is: What is the cause of fever?

THE CAUSE OF FEVER. Clinicians know from experience, that fever is always closely allied to infection, and that its intensity bears a direct relationship to the appearance of a new crop of microorganisms in the blood. The temperature of the malarial patient always rises after sporulation of the plasmodium. Lüdke also found that immediately preceding the rise in temperature, microörganisms are present in the blood of patients suffering with pneumonia and typhoid fever, although their blood was sterile the previous day. These facts at once suggested that the bacteria are responsible for the disturbances.

It was at first thought that the bacteria themselves by virtue of their presence, acted like foreign bodies, and produced irritation of the respiratory, circulatory, and heat regulating centres. In fact, it was demonstrated that the injection of a fine suspension of lycopodium or starch in the blood stream of animals produced a slight rise in temperature. But, it was soon seen that this theory did not work out in all cases We meet with a great many fevers where the infection is only local, and the disturbances are general. We meet with fever in cases of fractures, subcutaneous hemorrhages and resorption of blood, where there is no accompanying infection at all. These facts compelled investigations along entirely different lines.

Billroth[2] and Weber[3] injected the products of decomposed animal and vegetable substances into the blood stream of animals, and obtained the typical symptoms of fever, with circulatory, respiratory

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[1] Langenbeck's Arch., 1862, ii, 335.

[3] Berlin. klin. Woch., 1864, p. 39

and nervous disturbances. The injection of substances derived from the protoplasm of non-pathogenic germs produced similar results. Lüdke showed that an animal's own tissues ingrafted into itself, as well as foreign tissues, when absorbed, caused a rise in temperature. It was further shown that the injection of sterilized and filtered bacterial culture was followed by symptoms of intoxication. All these experiments show very clearly and definitely that although the bacteria themselves, by their presence in the tissues, may act as irritants, yet in the production of fever the presence of the toxin, produced by the bacteria, and the presence of substances of albuminous nature (Krehl), produced by the dissolution of the bacterial protoplasm or body cells are of far greater importance. These substances may contain more than one toxin, each having its own specific action. It was shown that the bouillon culture of tetanus bacilli contain in addition to the tetanus producing substances, a toxin which acts on the blood (hemotoxin). From the staphylococci we can isolate a substance leukocydin which has specific toxic influences on the leukocytes. In snake venom, we can isolate a neurotoxin, which acts on the nervous system, a hemolytic substance, hemorrhagin which acts on the endothelium of the bloodvessels, and thrombase which influences the fibrin.

Similar to some of the cells of the animal body, which possess a great many functions and produce a great many ferments, so the cells of bacteria have the power of producing a great many different substances which act injuriously on the human body. Although all have not yet been isolated and the specificity of each has not yet been determined, still it is hoped that they will be in the near future. We must not assume that all bacteria produce the different toxins in the same proportions, nor that all bacteria produce the same toxins. From the fact that the infections with different bacteria produce different reactions on the part of the leukocytes, immunity and formation of antibodies, we may safely conclude that the different species of bacteria contain and produce different toxins.

REGULATION OF BODY TEMPERATURE. The normal temperature of the body is maintained at a level, fluctuating between 36.5° to 37.5° C. It reaches its highest point at about 7 P.M., and its lowest point at about 6 A.M. Under normal conditions it seldom passes these limits. The most important factors which are responsible for the diurnal variations in temperature are work, the partaking of meals, and exposure to various stimuli. In fever, the temperature may go up to 41° and 42° C., and in some cases even higher. The factors which influence the normal temperature curve, act in a much more pronounced way in the febrile patient, and the chart presents much greater diurnal fluctuations. The height of the temperature in fever in a great many cases is proportional to the intensity of the intoxication, and may serve as a measure for it. But in the two extremes of life, childhood and old age, it cannot be relied upon. Mild infections in the child may be accompanied by very high temperature, whereas a most severe infection in the old, may produce a rise of only 1° or 2° C. (Krehl).[4]

The temperature of the normal individual is maintained at a constant level, because of the function of the heat regulating centre, which is situated in the anterior portion of the corpus striatum (Aronsohn und Sachs).[5] This centre stands in close nervous communication with every part of the body, and with all the vital centers in the medulla oblongata, especially the vasomotor centres.

All the vital processes in the cells of the body, be they secretion or motion, are the result of oxidation of organic matter in the cells. The oxidation of these substances is accompanied by generation of heat. This heat is utilized in keeping the body warm. It may be measured in terms of calories. One calory is the equivalent of the amount of heat that is necessary to raise one liter of water 1° C.

The human individual produces when at rest and under normal conditions, 33 calories per kilo. of his body weight every twenty-four hours. In other words, a man of 70 kilos will generate in the course of twenty-four hours, 2310 calories, that is, an amount of heat which will raise 23 liters of water from the freezing to the boiling point. Let this man do some work, and at once the oxidative processes will be increased, and more heat will be generated. All this heat is not retained in the body, but is given off into space. This is accomplished: (1) By radiation and conduction, and (2) by the evaporation of water from the skin and lungs.

It is at once apparent that the amount of heat lost by the body by radiation and conduction depends entirely upon the difference in temperature between the body and the surrounding atmosphere. To prevent the loss of too much heat in the lower animals, nature has supplied them with a coat of fur or feathers, which contain large quantities of stagnant air between. This stagnant air is a very poor conductor of heat. Civilized man resorts to an artificial method of protection against loss of too much heat. He covers his body with clothing, the character of which varies with the climate and the surrounding temperature. At this point we may accept without any reservation, the speculation of MacCallum[6] when he says, ". . . After all, it was this need of artificial heat regulation which probably brought about man's suddenly acquired knowledge of good and evil."

The temperature of the body can be maintained at a constant level only when there is complete calorific equilibrium, that is when the same quantity is eliminated as is produced. Should the heat elimination be greater than the heat production, there at once takes place a lowering of the body temperature. Should, however, the heat production be greater than the heat elimination, the temperature will rise. The function of the heat regulating centre is to prevent these variations.

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[4] Das Fieber, Pathologische Physiologie, 1910.

[5] Pflüger's Archiv, p. 37.

[6] Arch. of Internal Medicine, 1909

When a man is exposed to cold, a stimulation of the peripheral nerves takes place. This stimulation results in reflex contraction of the superficial bloodvessels. Less warm blood is brought to the skin, consequently, less heat is lost. Should the exposure continue and the physical process be inadequate for the protection against loss of heat, then a new factor is brought into play—the chemical process. All the muscles are thrown into fibrillary activity, shivering takes place, oxidation is thus increased, and a greater amount of heat is generated, enough to equal the loss. The body temperature remains unaffected.

If, however, the man is exposed to a tropical temperature, little or no heat can be lost by radiation and conduction, because the difference between the body temperature and the temperature of his environment is not great enough. A dilatation of the superficial bloodvessels and profuse perspiration takes place. This perspiration is evaporated, and every gram of water during the process of evaporation takes away 0.59 calories of heat from the body. We see from the experiments performed by Rubner[7] that a man, who was exposed to a temperature of 20° C., evaporated 56 gm. of water per hour. When he was exposed to a temperature of 36° to 37° C., his body temperature being equal to the temperature of the surroundng atmosphere, he could lose no heat by radiation and conduction. The amount of water then evaporated per hour rose to 204 gms. These 204 gms. of water per hour required 120.3 calories, to evaporate. For the twenty-four hours, a total of 2888 calories, the equivalent of the total amount of heat produced by that man. The man's temperature remained constant. This is a good illustration of how perfectly the heat regulating centre acts. It may be stated here, that R. Cohn succeeded in producing dilatation of the bloodvessels and secretion of sweat, by simply raising the temperature of the blood of the carotid arteries on its way to the brain.

THE MECHANISM OF FEVER. Having considered the physiology of the temperature regulation, we will take up the subject of the mechanism of fever. It is evident from what was said above, that the rise in temperature in fever can be accomplished only by a disturbance in the balance between heat production and heat loss. There are two possibilities, therefore. Either there is an increase in heat production without a corresponding increase in heat loss, or there is no increase in heat production, but there is diminution in heat loss. In either case a storing of heat in the body will take place. An enormous amount of work has been done on this subject in the past number of years, and the results are very conflicting, undoubtedly due to the differences in the methods employed by the different investigators. Time does not allow us to enter in any detailed discussion of these methods and their respective results. I shall only summarize the work which is most complete and very convincing. This work was performed by Likhachev and Avroroff,[8] in Paschutins Laboratory, in St. Petersburg.

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[7] Die Gesetze des Energieverbrauchs bei die Ernärung, 1902.

They studied the metabolism of a young Russian woman who was afflicted with malaria. She was placed in an oval shaped calorimeter which had a capacity of 2.7 cubic meters. She was made comfortable by being placed on a bed close to the floor. The calorimeter was kept hermetically sealed. Eighty liters of air were driven through the calorimeter per minute, and were made to pass through sulphuric acid for the determination of water, and through potassium hydrate for the determination of carbon dioxide given off by the patient. Before the experiment was begun, the patient was weighed, her food and water for drinking were measured out. After she had been installed and sealed in the calorimeter, ventilation was carried on for one to two hours until an equilibrium in temperature was established. The other twenty-two hours of the twenty-four were divided into eleven two-hour periods. At the end of every hour the patient's temperature was ascertained, also the temperature of the room, air, and of the calorimeter. At the end of every period the weight of the CO_2 and water given off were determined, also the amount of air that passed through the calorimeter and its temperature.

The heat lost by radiation and conduction was determined by noting the changes in the temperature of the calorimeter and the changes in the temperature of the air that passed through it. The heat lost by evaporation of water was measured by determining the quantity of water given off by the patient through her skin and lungs, and by multiplying same by 0.59 calories. The total heat production was obtained from the sum of the values of the heat lost by evaporation of water and by radiation and conduction plus or minus the retention or loss of heat because of changes in the body temperature. This last one was determined from the following formula: $W \times (T \pm t) \times S$. W equals body weight, T equals temperature of body, t equals value of change in temperature, and S equals specific heat of body, which equals 0.83.

The patient was kept in the calorimeter for three days, one normal and two febrile. The results are here tabulated. See table I and Figs. 1 and 2.

The patient was at perfect ease while in the calorimeter. We see from the curve of the normal day, that the heat production fluctuates from 85 calories per hour to 46 calories, and that the total heat elimination throughout the day runs approximately parallel to the former. We also notice that the greatest amount of heat,

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[8] Isviesti Imperatorskoy Voenno Medicinskoi Academii, 1902, v. 239. I am indebted to Prof. F. G. Benedict for kindly calling my attention to this work, which was published in 1902, and remained entirely unknown to the western world.

74.6 per cent., is lost through radiation and conduction, and that only 25.4 per cent. is lost by evaporation of water.

On the day of high fever, at midnight the patient was placed in the calorimeter. During the morning, she presented the typical symptoms of malaria. At 1 A.M., the chill set in which lasted for about two hours. The heat production per hour thus rose from 54 calories to 93. The heat elimination, however, sank from 65 calories per hour to 57. This tremendous disturbance in the balance between heat production and heat loss resulted in heat being stored in the body, and the body temperature rose from 36, to 38, 39, and finally to 39.7° C. These results led the experimenters to conclude that the rise of temperature in fever is due to an increase in the heat production without a corresponding increase in heat elimination.

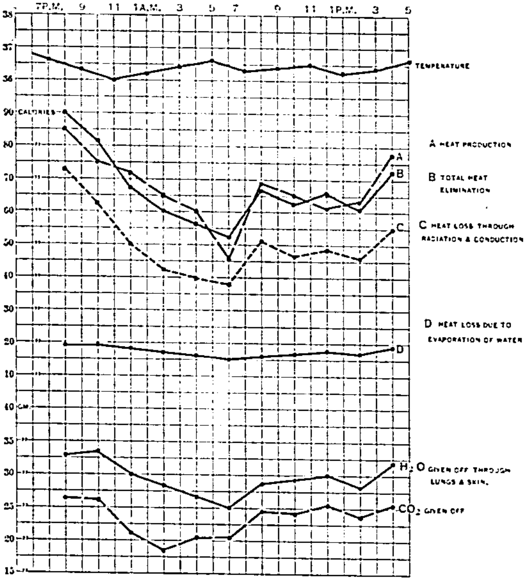

FIG. 1.—Normal day.

This increase in heat production is most marked during the period of the initial chill. In long continued fevers, some authors believe there is an increase in heat production only in so far as there is an increase in the activity of the respiratory muscles and heart beat. Matthes,[9] however, believes that after subtracting the heat produced by the increased activity of the respiratory muscles and increased heart beats, and by subtracting the increased heat produced, due to rise in body temperature, there will still be found an increase above the normal. This increase, he believes, is caused by the toxins themselves. As a matter of fact, Krehl and Soetbeer found an increase in heat production in infected cold-blooded animals.

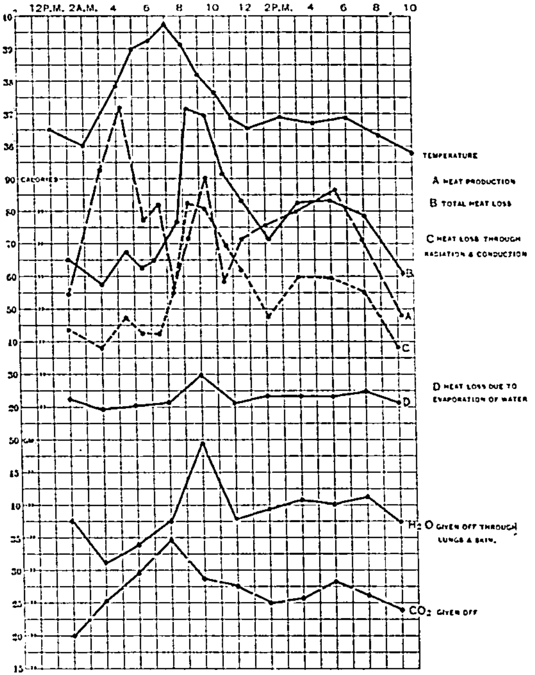

Fig. 2.—Day of high fever.

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[9] Ueber das Fieber; Die Deutsch. klin. am Eingange des Zwanzigsten Jahrhunderts, 1909, p. 1.

TABLE I.

Condition.	Total heat production. Calories.	Maximum heat production per hour. Calories.	Minimum heat production per hour. Calories.	Heat lost by radiation and conduction. Per cent.	Heat lost by evaporation of H_2O. Per cent.	Food value in calories.	CO_2 given off in grams.	H_2O evaporated from skin and lungs in grams.	O_2 consumed in grams.	R. Q.	Amount of urine. Grams.	N in urine.	C in urine.	Body temperature. (C.)
Normal	1480	91.0	53.0	74.6	25.4	1030	513.0	637.0	400.0	0.92	1790.0	11.4	8.8	30.0 to 30.7
Low fever	1492	78.0	50.6	74.7	25.3	776	520.0	638.0	474.0	0.8	412.0	9.1	7.5	
High fever	1633	112.0	48.0	69.8	30.2	533[1]	587.0	852.0	503.0	0.76	593.0	10.2	0.0	35.8 to 30.7

[1] The food taken on this day is almost one-half of normal. This influences heat production a great deal by eliminating the specific dynamic action of that food.

TABLE II.—Bacilli in 100 Leukocytes.

Temperature.	Typhoid B.	Streptococci.	Staphylococci.	Tubercle B.
30° C.	1080	1400	1210	1110
37 to 37.5	1100	1520	1200	1400
38.5	1120	1500	1590	1580
35.9 to 40	1530	1650	3100	1800
41.5	1040	....	1150	
42.5	010	760		

The cause of the accelerated pulse and respiration during fever can be found partly in the overheating of the body. But we must not exclude the possibility of a specific toxin acting on the cardiac and respiratory centres. The fact that the character of the pulse and its rate are different in different diseases, that it is always slow in typhoid, and very rapid in sepsis, speaks very much in favor of this possibility.

THE EFFECT OF HIGH TEMPERATURE. It was the belief of the early investigators (Liebermeister, Littern), that the high temperature in fever produced deleterious influences on the organism, and that the fatty and parenchymatous degenerations were due to it. This belief was practically universal, and in the matter of treatment of febrile patients, it was always borne in mind. The works of Naunyn[10] and Unverricht,[11] based upon clinical and experimental observation destroyed these theories. Naunyn showed that animals can be kept for weeks at a febrile temperature without presenting any signs of degeneration. As soon as this was corroborated and the conviction of the harmfulness of the high temperature removed, investigators began to inquire into the purpose of the high temperature in fever. The application of the Darwinian doctrine of the "preservation of the useful" to this case, was energetically opposed by Krehl,[12] who showed that this theory cannot be used in explaining pathological processes.

Rolly and Meltzer,[13] and later Lüdke,[14] studied the influence of the febrile temperature on the different components of the reaction toward infection. Namely, its influence: (1) On the growth of bacteria in the animal body; (2) on the resistance of animals toward bacterial infection; (3) on the bactericytic power of the blood; (4) on phagocytosis; (5) on the bacterial toxins; (6) on the production of antitoxins.

The hyperthermia was brought about by placing the animals in well ventilated, double-walled metal cages, which were kept at a temperature of about 35° to 36° C. by means of a burning flame. This flame was regulated by means of a thermoregulator which was situated between the walls of the cages. The animal's temperature under those conditions rose to about 40° C. The animals that were overheated, after receiving daily subcutaneous injections of one-fourth to one-half the fatal dose of either staphylococci, pneumococci, or bacilli coli communis, lived longer and one-half of them survived, whereas all of the control animals died.

The influence of the febrile temperature on phagocytosis is shown beautifully in Table II.

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[10] Arch. f. Experimentelle Pathologie und Pharmacologie, 1884, xviii, 49.

[11] Deutsch. med. Wochenschr., 1883, vol. v.

[12] Lubarsch Ostertags Ergebnisse, 1896.

[13] Deutsch. Arch. f. klin. Med., 1908, xciv, 335.

[14] Ibid., 1909, xcv, 425.

THE TREATMENT OF FEBRILE CONDITIONS.[1]

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It is one of the most hopeful features of modern therapy that it is taking cognizance of the fact that the organism has been perfecting means of defense since first it became the seat of disease and that these means of defense are to be read not merely in the subtile elaboration of antitoxic bodies in the tissues and the marshalling of counter-forces in the blood elements, but also in the alteration of the functions of organs. Emesis as a symptom is primarily an effort to unburden the stomach of deleterious substances; diarrhea is protective in the same sense; cough removes secretions which are both irritants and mechanical impediments to the respiration; pain ensures rest to an affected part and so on. Interference with these symptoms must be undertaken with discretion lest it become pernicious. It is the knowledge of when to let alone and when to interfere that constitutes the art of therapy. Emesis, diarrhea and cough may become a source of exhaustion; pain which has pointed the way to the trouble and hinted the need of rest be illy borne when continued and fever arise to degrees that are incompatible with its purpose and constitute hyperpyrexia. At this point, treatment steps in to modify and assist, not to disregard Nature's signals.

Fever, as the physician knows it, is almost invariably the result of bacterial action, so cannot be dissociated from toxemia; but pyrexia and toxemia show but little parallelism; indeed, the worst forms of toxemia may be accompanied by no pyrexia at all, while a relatively high temperature may be seen with a minimal toxemia. Briefly, then, unless the degree of temperature is inordinately high, that is, constitutes a hyperpyrexia, the treatment of fever is not an antipyretic treatment but an antitoxemic treatment, and such fall of temperature as accompanies our efforts is incidental to them and not the object at which we aimed.

The treatment of fever,involves the appreciation of certain broad principles that in the main are physiological. They are not numerous, but they are of fundamental importance. We shall take them up seriatim. (1) rest; (2) diet, including the ingestion of water; (3) fresh air; (4) water locally applied, that is hydrotherapy; (5) drugs; (6) hyperpyrexia. I think it little matters what name we give the febrile process or the organism inducing it. The procedures are much the same.

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[1] Read before the Eastern Medical Society, New York City.